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ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,449	ARCOT, SANTOSH S.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-29,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-29,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's RCE and the amendment filed on February 10, 2004 have been entered. The claims pending in this application are claims 3, 5-29, 35, and 36. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on November 24, 2004.

Specification

2. In previous office action, the examiner indicated that "the substitute specification filed May 2, 2003 has not been entered because it does not conform to 37 CFR 1.125(b) and (c) since applicant does not filed a clean copy without markings.". However, applicant does not address this issue in the amendment filed on November 24, 2004.

Claim Objections

3. Claims 3 and 5 are objected to because of the following informality: from the claims, it appears that two contacting step (one is in the beginning and another one is in the last paragraph of the claims) are identical, the examiner suggests applicant to cancel one of contacting steps.

Response to Arguments

In page 23, second paragraph bridging to page 24, second paragraph of applicant's remarks filed on November 24, 2004, applicant argues that "[W]ith regard to the allegations of paragraph 2, Applicant submits respectfully that the 'contacting step' recited at the beginning of each of the claims is not identical to the contacting step in the last paragraph of each of the claims. In each case, the contacting step at the beginning of the claim is recited as part of a general description of the method of claim, and the second recitation of the contacting step is a more precise description of the contacting step as applied particularly to each claim. For example, in Claim 3, the last paragraph limits the general contacting step at the beginning of the paragraph to particular conditions wherein each of the target nucleic acid sequences have different sequences in their first potion, but substantially identical sequences in their second portion. Accordingly, in this example, the spectrally-addressable bound probes have different sequences one from another, but the free probes have substantially identical nucleotide sequences. The general description would allow the free probes to have different sequences, one from another. Conversely, in Claim 5, the later description of the contacting step provides that the spectrally-addressable bound probes substantially identical nucleotide sequences whereas the free probes have different sequences, one from another. The general description would allow the bound probes to have different sequences, one from another.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the objection because applicant does not explain why claims 3 and 5 require a general contacting step and a particular contacting step which are not correspond each other. One skill in the art will have difficult to understand why a method recited in claims 3 and 5 need have two contacting steps which are not correspond each other.

4. Claim 10 is objected to because of the following informalities: (1) "a nucleotide at the opposite end" should be "a nucleotide at one of the opposite ends"; (2) "another portion" in (ii) of step (a) should be changed since there is no phrase "one portion" before "another portion"; and (3) "a unique" in (iii) of step (a) should be "an unique".

5. Claim 22 is objected to because of the following informality: "a given set" should be "the given set".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 3, 5-29, 35, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 3 and 5 are rejected as vague and indefinite in view of the phrase " one or both of detecting the presence of the spectrally addressable ligated products or analyzing the nucleic acid sequence of the spectrally-addressable ligated products" because it is unclear what it intended. "one or both of " in the phrase needs to be deleted in order to understand the phrase. "one or both of' in the phrase causes the phrase confusing. Please clarify.

9. Claim 3 is rejected as vague and indefinite because the beginning of the claim and the end of the claim do not correspond each other. The beginning of the claim requires that a sample

suspected of containing one target nucleic acid sequence contacts with one subset of spectrally-addressable bound probe. However, the end of the claim requires two target nucleic acid sequences (first and second target nucleic acids) and two subsets of spectrally-addressable bound probes. Please clarify.

10. Claim 5 is rejected as vague and indefinite because the beginning of the claim and the end of the claim do not correspond each other. The beginning of the claim requires that a sample suspected of containing one target nucleic acid sequence contacts with one subset of free probe. However, the end of the claim requires that two target nucleic acid sequences (first and second target nucleic acids) and two subsets of spectrally-addressable bound probes. Please clarify.

Response to Arguments

In page 17, third paragraph of applicant's remarks filed on November 24, 2004, applicant argues that "[T]he Final Office Action alleges that the beginning and end of each claim do not correspond to each other. The Final Office Action alleges that the beginning of each of the claims recites, variously, only one target nucleic acid, free probe, or bound probe, whereas the end of each of the claims recites, variously, two target nucleic acids, free probes, or bound probes. Applicants traverse respectfully. Applicant directs Examiner's attention to the first paragraph following the preamble of each of Claims 3 and 5, wherein the claims recite 'one or more target nucleic acid sequences with one or more subsets of free probes and one or more subsets of spectrally-addressable bound probes' (emphasis added). In view of the claims' recitation, Applicant submits respectfully that the Final Office Action is in error with regard to the allegations of paragraphs 8 and 9.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because "contacting one or more target nucleic acid sequences with

one or more subsets of free probes and one or more subsets of spectrally-addressable bound probes" can be read as "contacting one target nucleic acid sequences with one subset of free probes and one subset of spectrally-addressable bound probes".

11. Claim 8 is rejected as vague and indefinite. Since the same amount of fluorescent dye is incorporated into each bound probe in each subset, each bound probe should have the same amount of fluorescent dye. The phrase "but wherein each subset of bound probes incorporates a distinctly different amount of fluorescent dye, and one subset of spectrally-addressable bound probes is distinguishable from other subsets of spectrally-addressable bound probes based at least on the relative amount of the at least one fluorescent dye incorporated into the spectrally-addressable bound probe of the subset" in incorrect. Please clarify.

12. Claim 10 is rejected as vague and indefinite because it is unclear whether "the free probes of a given set" in (ii) of step (a) is identical to least one set of free probes in (i) of step (a) or not. Please clarify.

13. Claim 10 is rejected as vague and indefinite because it is unclear whether "the free probes of a given set" in (i) of step (a) is identical to least one set of free probes or not. If "the free probes of a given set" in (i) of step (a) is identical to least one set of free probes, "the free probes of a given set" should be the least one set of free probes. Please clarify.

14. Claim 10 is rejected as vague and indefinite in view of (i) of the step (a) because it is unclear that a detectable label is at one of two opposing ends or not. Please clarify.

15. Claim 10 is rejected as vague and indefinite because it is unclear whether "a given subset of bound probes" in (ii) of step (a) is identical to least one subset of bound probes or not. If "a given subset of bound probes" in (ii) of step (a) is identical to least one subset of bound probes,

"a given subset of bound probes" should be "the least one subset of bound probes". Please clarify.

16. Claim 10 is rejected as vague and indefinite in view of (iii) of step (a). Since fluorescence intensity is one of properties of a fluorescent dye, it is unclear what means the microspheres of bound probes of a given subset having an unique fluorescence intensity. Furthermore, it is unclear what means "one" in the phrase "which allows one to distinguish the microspheres of a given subset from those of another". Does "one" in the phrase "which allows one to distinguish the microspheres of a given subset from those of another" means one having ordinary skill in the art? Please clarify.

17. Claim 16 is rejected as vague and indefinite because it is unclear that, if the bound probes differ in that the nucleotide found at one end of oligonucleotide probes of one subset differs from that found at the corresponding end of oligonucleotide probes of the other subset" , how the nucleotide sequences comprising the oligonucleotide probes of the at least two subsets of bound probes are otherwise substantially identical. Therefore, the first part of the claim and the second part of the claim does not correspond each other. Furthermore, it is unclear what means "the corresponding end of oligonucleotide probes". Please clarify.

18. Claim 20 is rejected as vague and indefinite because it is unclear what it intended. The phrase "the nucleotide and the detectable label found at opposite ends of the free probes of one set differing from that nucleotide and the detectable label found in the corresponding ends of the free probes of the other set" is unclear because, from claim language of this phrase, it is unclear that "opposite ends of the free probes" recited in claim 20 are identical to two opposing ends in claim 10 or not. If "opposite ends of the free probes" recited in claim 20 are identical to two opposing ends in claim 10, "opposite ends of the free probes" recited in claim 20 should be "the

opposite ends of the free probes". Furthermore, it is unclear what means "corresponding ends of the free probes". Please clarify.

19. Claim 20 is rejected as vague and indefinite because it is unclear, if at least two sets of free probes are different, how the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical. Therefore, the first part of the claim and the second part of the claim do not correspond each. Please clarify.

20. Claim 20 is rejected as vague and indefinite since claim 10 and 20 does not correspond each other since the mixture in claim 10 comprises at least one set of free probe (ie., one set of free probe) while the mixture in claim 20 contains at least two set of free probes (ie., two set of probes). Please clarify.

21. Claim 23 is rejected as vague and indefinite because it is unclear, if at least two subsets of bound probes are different, how the nucleotide sequences comprising the at least two subsets of bound probes are otherwise substantially identical. Therefore, the first part of the claim and the second part of the claim do not correspond each. Please clarify.

22. Claim 24 is rejected as vague and indefinite because it is unclear, if at least two sets of free probes are different, how the nucleotide sequences comprising the at least two sets of free probes are otherwise substantially identical. Therefore, the first part of the claim and the second part of the claim do not correspond each. Please clarify.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

24. Claims 3, 5, 7, 9-27, 29, 35, and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Chee *et al.*, (US Patent No. 6,355,431, priority date: April 20, 1999).

Claims 3 and 5 are rejected in view of the ambiguity of claims since it is unclear what they intended (see above rejections under 35 USC 112, second paragraph).

Chee *et al.*, teach detection of nucleic acid amplification reaction using bead arrays.

Regarding claims 3, 5 and 9, Figures 7A, 7B, 7C, 7D, 7E and 7F shows a method of OLA/RCA (the oligonucleotide ligation assay/rolling circle amplification). First, a first OLA primer 45 bound to microsphere 10 is hybridized with a target sequence 25 and a second OLA primer 50. Following the addition of ligase, the first and second OLA primers are ligated to form a ligated oligonucleotide 56 (modified primer nucleic acid). Following denaturation to remove the target nucleic acid, the immobilized ligated oligonucleotide is distributed on an array. The immobilized ligated oligonucleotide (modified primer nucleic acid) is detected or is used in RCA wherein an RCA probe 57 and polymerase are added to the array resulting in amplification of the circular RCA probe 58 as recited in claim 9. The modified primer comprises a detectable label, such as a fluorescent label, which is either incorporated by the enzyme or present on the original primer (see columns 3-7, 11, and 44 and claims 1-13 in columns 59-61). Note that the first OLA primer 45 is considered as a spectrally-addressable bound probe while the second OLA primer 50 is considered as a free probe. Chee *et al.*, also teach that the method comprises hybridizing at least a first primer nucleic acid to a first target sequence to form a first hybridization complex, and hybridizing at least a second primer nucleic acid to a second target sequence that is

substantially complementary to the first target sequence to form a second hybridization complex (see column 4). Since the second target sequence is substantially complementary to the first target sequence, the sequence of the first primer nucleic acid must be different from that of the second primer nucleic acid. Since these first and second primers can attach to microspheres (see Figures 7A to 7F), they are considered as two subsets of bound probes that are distinguishable from each other as recited in claim 3. According to the definition in the specification (see page 9), "substantially identical" means that, when used in connection with the phrase nucleotide sequence, "one or more nucleotides at one or more positions of probes in a subset may differ due to one or more substitutions, insertions, deletions, or combinations thereof but can still be distinguished from probes belonging to another subset and can substantially hybridize to the correct position on the target molecule,". Since these first and second primers have differences in one or more positions and they also consider to be substantially identical as recited in claim 5. Chee *et al.*, also teach that the third primer hybridizes to a second adjacent domain of the first target nucleic acid while the fourth primer hybridizes to a second adjacent domain of the second target nucleic acid (see column 60). Since the second target sequence is substantially complementary to the first target sequence, the sequence of the third primer nucleic acid must be different from that of the fourth primer nucleic acid. Since the third and fourth primer nucleic acids are considered as free probes here, one subset of free probe (the third primer nucleic acid) is distinguishable from other subsets of free probe (the fourth primer nucleic acid). Since these third and four primers have differences in one or more positions and they also consider to be substantially identical as recited in claim 3 according to the definition of "substantially identical". Although claim 3 appears to require two subsets of bound probes and one subset of free probe and claim 5 appears to require two subsets of free probes and one subset of bound

probe, since Chee *et al.*, teach two subsets of free probes and two subset of bound probes (see above) and claims 3 does not limit the claim to only two subsets of bound probes and only one subset of free probe while claim 5 does not limit the claim to only two subsets of free probes and only one subset of bound probe, two subsets of free probes and two subset of bound probes taught by Chee *et al.*, meet the scope of two subsets of bound probes and one subset of free probe as recited in claim 3 or one subsets of bound probe and two subsets of free probes as recited in claim 5. Therefore, claims 3 and 5 are anticipated by Chee *et al.*.

Regarding claim 10, as shown in Figures 7A to 7F, Chee *et al.*, teach: (a) contacting a sample, which is suspected of containing target nucleic acid molecules having a certain nucleotide sequence, with a mixture comprising at least one set of free probes (ie., a second OLA primer 50) and at least one subset of bound probes (ie., a first OLA primer 45), wherein (i) the free probes of a given set comprise two opposing ends with a detectable label at one of their ends (ie., see column 11, last paragraph for the original primer with a fluorescent label) and a nucleotide at the opposite end and an oligonucleotide having a predetermined nucleotide sequence that is complementary to at least a portion of the target nucleic acid molecules (see Figure 7B); (ii) the bound probes comprise a microsphere and an oligonucleotide probe wherein the oligonucleotide probes of a given subset of bound probes further comprise an oligonucleotide at one of their ends having a modifier moiety (ie., amino groups, see column 43, last paragraph bridging to column 44, first paragraph) which is used for coupling the oligonucleotide probe to the microsphere (see column 43) and wherein the oligonucleotide probe further comprises an oligonucleotide having a predetermined nucleotide sequence that is complementary to at least another portion of the target nucleic acid molecules (see Figure 7B); and (iii) the microspheres of bound probes of a given subset having an unique spectral address or an unique fluorescence dye

which allows one to distinguish the microspheres of a given subset from those of another (see columns 44 and 45); (b) allowing the free probes and the bound probes to hybridize to the target nucleic acid molecules (ie., see Figure 7B); (c) ligating one of the ends of the free probes with one of the ends of the bound probes to provide microsphere-bound ligated products (see Figure 7C); and (d) detecting the presence of microsphere-bound ligated products (see Figures 7D to 7F, and column 6, last paragraph bridging to column 7, first paragraph).

Regarding claim 7, the ligase used in OLA taught by Chee *et al.*, is considered as a thermostable ligase since the ligation reaction is performed in a certain temperature in order to maximize the activity of the ligase.

Regarding claims 11 and 12, since the free probes and bound probes bind to different region of the target nucleic acids (see Figures 7A to 7F), Chee *et al.*, teach claims 11 and 12.

Regarding claims 15-21, since two subsets of free probes have different sequences while two subsets of bound probes with microspheres have different sequences, according to the definition of "substantially identical" (see above and column 10, third paragraph), Chee *et al.*, teach claims 15-21.

Regarding claims 13, 14, and 22-24, as shown in Figures 7A, 7B, 7C, and 7D, since the second OLA primer 50 (free probe) is 3' of the first OLA primer 45 and 3' -OH of the first OLA primer 45 ligates with phosphate group of the second OLA primer 50 in the presence of a DNA ligase (see attachment in previous office action) to form a 3', 5' phosphodiester bond, Chee *et al.*, teach the free probe comprises a phosphate at the other of its end (5' end of the second OLA primer 50). Since 5' end the second OLA primer 50 (free probe) is used for the ligation reaction and its fluorescence label must be in its 3' end and the first OLA primer 45 with modified moiety comprising an primary amino group, Chee *et al.*, teach claim 22 because the phrase "which

couples the 5' end of the oligonucleotide of the bound probe to a carboxylic acid group on the microsphere" is only considered as an ability of the modified moiety. Since 5' of the first OLA primer 45 has a phosphate, claim 14 is anticipated by Chee *et al.*. Since two subsets of free probes have different sequences while two subsets of bound probes with microspheres have different sequences, according to the definition of "substantially identical", Chee *et al.*, teach claims 23 and 24.

Regarding claims 25, 26, and 29, since Chee *et al.*, teach that, after the ligation, the immobilized ligated oligonucleotide is denatured to remove the target nucleic acid and then distribute on an array. Finally the immobilized ligated oligonucleotide (modified primer nucleic acid) is detected (see lines 33-47 in column 3). Since above ligation and detection are carried out in a separate reaction vessel, Chee *et al.*, teach claim 26. Alternatively, since Chee *et al.*, teach that, after the ligation, the mixtures is added a second enzyme, a polymerase such that the circular probe is amplified in a rolling circle amplification (RCA) assay (see lines 58-65 in column 3). Since, in the alternative assay, ligation and detection are carried out in a single reaction vessel, Chee *et al.*, teach claims 25 and 29.

Regarding claim 27, since a microspheres with an unique signature such as fluorophore can distinguished from beads with different optical signatures and fluorophores have different signal intensity (ie., emission intensity) based on an excitatory stimulus, Chee *et al.*, teach claim 27.

Regarding claims 35 and 36, since the microsphere includes amino groups including aliphatic and aromatic amines (see lines 65-67 in column 43 and lines 1-3 in column 44), Chee *et al.*, teach the bound probe comprising a microsphere with a modified moiety wherein the modified moiety comprises an primary amino group as recited in claims 35 and 36.

Therefore, Chee *et al.*, teach all limitations recited in claims 3, 5, 7, 9-27, 29, 35, and 36.

Response to Arguments

I. In page 14, second paragraph bridging to page 15, first paragraph of applicant's remarks, applicant argues that "[T]he Final Office Action cites this passage as an example of identifying multiple target sequences. The Final Office Action notes, correctly, that complementary sequences are different. However, the Final Office Action alleges that, since these primers can attach to microspheres, they are considered as two subsets of bound primers. Without acquiescing in the allegation that both primers may be bound to microspheres, Applicant submits respectfully that both primers are not disclosed as being bound to microspheres', accordingly they do not teach two subsets of bound probes. Furthermore, the Final Office Action alleges that primers that are complementary to each other are substantially identical. Applicant submits respectfully that one skilled in the are would recognize that complementary sequences are, by definition, completely different from each other except for rare palindromic sequences. The Final Office Action alleges that Applicant's definition of "substantially identical" sequences allows that such sequences may contain some differences. However, as the Examiner admits in line 5 of page 12 of the Final Office Action, substantially identical nucleotides bind to the same sequence. By definition, complementary sequences bind each other, not the same sequence (except in the case of palindromic sequences, such as restriction sites). Accordingly, complementary sequences cannot be substantially identical.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, claims 3 and 5 are rejected in view of the ambiguity of claims since the beginning of the claims and the end of the claims do not correspond each other. In claim 3, the beginning of the claim requires that a sample suspected of containing one target

nucleic acid sequences contacts with one subset of spectrally-addressable bound probe. However, the end of the claim requires two target nucleic acid sequences and two subsets of spectrally-addressable bound probes (see previous rejections under 35 USC 112, second paragraph). It is not unclear whether the claim 5 requires two subsets of spectrally-addressable bound probes or not. Second, according to the specification (page 9), "substantially identical" means that, when used in connection with the phrase nucleotide sequence, "one or more nucleotides at one or more positions of probes in a subset may differ due to one or more substitutions, insertions, deletions, or combinations thereof but can still be distinguished from probes belonging to another subset and can substantially hybridize to the correct position on the target molecule," complementary sequences can be substantially identical since complementary sequences can have more than one substitutions, can still be distinguished each other and can substantially hybridize (ie., partially) to the correct position on a target molecule.

II. In page 15, last paragraph of applicant's remarks, applicant argues that "with respect to Claim 9, the Final Office Action alleges that amplification of the target sequence by RCA (rolling circle amplification) anticipates the PCR amplification of Claim 9. One skilled in the art will recognize immediately that RCA and PCR are two entirely different processes. Also, the Final Office Action suggests that the thermostable ligase claimed in Claim 7 is anticipated by the ligase used in Chee's OLA because the ligation reaction is performed at a temperature that optimizes the activity of the ligase. One skilled in the art will recognize immediately that a thermostable ligase is one that can withstand temperatures approaching or exceeding the 100 degrees Celsius, as can the thermostable polymerases disclosed by Chee, not a ligase that has an optimal temperature. Chee does not disclose thermostable ligase."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner agrees with applicant that "RCA and PCR are two entirely different processes.". However, claim 9 is not directed to a PCR method but is directed to polymerase chain reaction components which are also used in RCA. Second, one skilled in the art will not recognize immediately that a thermostable ligase is one that can withstand temperatures approaching or exceeding the 100 degrees Celsius since claim 7 does not define that a thermostable ligase is one that can withstand temperatures approaching or exceeding the 100 degrees Celsius.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee *et al.,* (March 3, 2000) as applied to claims 3, 5, 7, 9-27, 29, 35, and 36 above, and further in view of Kwok *et al.,* (US Patent No. 5,945,283, published on August 31, 1999).

The teachings of Chee *et al.,* have been summarized previously, *supra.*

Chee *et al.,* do not disclose that the assay is performed in a first and a second reaction vessel, a portion of the sample is contacted with the first subset of free probes in the first reaction vessel and a portion of the sample is contacted with the second subset of free probes in the second reaction vessel as recited in claim 6.

Kwok *et al.,* teach to test two nucleic acid samples in separate reaction vessels (see

column 5, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the assay recited in claim 5 in a first and a second reaction vessel wherein a portion of the sample is contacted with the first subset of free probes in the first reaction vessel and a portion of the sample is contacted with the second subset of free probes in the second reaction vessel in view of the patents of Chee *et al.*, and Kwok *et al.*. One having ordinary skill in the art would have been motivated to do so because Kwok *et al.*, have successfully test two nucleic acid samples in separate reaction vessels and performing the assay recited in claim 5 in separate reaction vessels would enhance to use a single sample for multiple purposes and save laboratory cost. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the assay recited in claim 5 in separate reaction vessels.

27. Claims 8 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to Chee *et al.*, (March 3, 2000) as applied to claims 3, 5, 7, 9-27, 29, 35, and 36 above, and further in view of Church *et al.*, (US Patent No. 6,485,944 B1, filed on March 12, 1999).

The teachings of Chee *et al.*, have been summarized previously, *supra.*

Chee *et al.*, do not disclose that each subset of bound probes incorporates a distinctly different amount of fluorescent dye, and one subset of spectrally-addressable bound probes is distinguishable from other subsets of spectrally-addressable bound probes based at least on the relative amount of the at least one fluorescent dye incorporated into the spectrally-addressable bound probe of the subset as recited in claim 8 and that the spectrally addressable microspheres of one subset can be distinguished from the spectrally addressable microspheres of another

subset by the relative amounts of at least two fluorescent dyes harbored by the spectrally addressable microspheres as recited in claim 28.

Church *et al.,* teach that, when a first and a second nucleic acid probes are labeled with a first and a second fluorescent dyes, the relative amount of the first fluorescent dye and the second fluorescent dye is used to detect the amount of a RNA expression in a first RNA-containing nucleic acid population relative to that expressed in a second RNA-containing nucleic acid population (see column 2, fifth paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 wherein each subset of bound probes incorporates a distinctly different amount of fluorescent dye, and one subset of spectrally-addressable bound probes is distinguishable from other subsets of spectrally-addressable bound probes based at least on the relative amount of the at least one fluorescent dye incorporated into the spectrally-addressable bound probe of the subset as recited in claim 8 or have performed the method recited in claim 10 wherein the spectrally addressable microspheres of one subset can be distinguished from the spectrally addressable microspheres of another subset by the relative amounts of at least two fluorescent dyes harbored by the spectrally addressable microspheres in view of the patents of Chee *et al.,* and Church *et al.*. One having ordinary skill in the art would have been motivated to do so because Church *et al.,* have successfully detected relative amount of two nucleic acids using the relative amount of the first fluorescent dye and the second fluorescent dye (see Church *et al.,* column 2, fifth paragraph) and the simple replacement of one well known fluorescence detection method (i.e., the method taught by Chee *et al.,*) from another well known fluorescence detection method (i.e., using the relative amount of the first fluorescent dye and the second fluorescent dye by Church *et al..,*) during the

process of performing the method recited claim 3 or performing the method recited in claim 10 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the fluorescence detection method taught by Chee *et al.*, and the fluorescence detection method taught by Church *et al.*, are functional equivalent methods which are used for the same purpose (ie., detection of nucleic acid hybridization).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Conclusion

28. No claim is allowed.

29. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
April 19, 2004

FRANK LU
PATENT EXAMINER